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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66,70-75 and 78-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66,70-75 and 78-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 8/30/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/2/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

Applicant has added claims 83-98. Therefore, claims 66, 70-75 and 78-98 are pending in the application.

Applicant's arguments and/or amendments filed on 8/30/07 have been considered but are not persuasive. Furthermore, upon further consideration, a new ground(s) of objection and/or rejection is made in view of the instant amendments.

Response to Claim Rejections - 35 USC § 112

Claims 66, 70-75 and 78-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of record as explained in the office action mailed on 5/2/07. Newly added claims 83-98 are rejected for the same reasons. **This is a new matter rejection.**

The claims are directed to an oligonucleotide wherein "said oligonucleotide comprises a 20 nucleobase portion having a gap segment, a first wing segment and a

second wing segment, said gap segment consisting of ten contiguous 2'-deoxy nucleosides flanked on its 5' and 3' ends by said first and second wing segments, each of said first and second wing segments independently consisting of five 2'-O-methoxyethyl nucleosides" or "said oligonucleotide comprises a 20 nucleobase portion having a gap segment, a first wing segment and a second wing segment, said gap segment consisting of twelve contiguous 2'-deoxy nucleosides flanked on its 5' and 3' ends by said first and second wing segments, each of said first and second wing segments independently consisting of four 2'-O-methoxyethyl nucleosides", which constitutes new matter. The specification does not contemplate these limitations and hence does not provide support for such.

Furthermore, there is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 5/20/99, which is the filing date of the instant application.

Applicant's arguments filed 8/30/07 point to support for the amendments to the claims on pages 31-34, particularly lines 9-25 of page 34 of the instant specification. A review of the specification, and particularly at pages 31-34 and lines 9-25 of page 34, does not reveal support for where the various claim amendments are found.

Pages 31-33 of the instant specification offers general support for chimeric oligonucleotides including gapmers with 2'-O-methoxyethyl-2'-deoxy-2'-O-methoxyethyl and phosphorothioate configurations, but does not disclose any specific size limitations for the 2'-O-methoxyethyl wing segments or 2'-deoxy gap segments.

Lines 9-25 of page 34 disclose nine specific oligonucleotides and target genes to which they inhibit. Of the nine specific oligonucleotides, one of the oligonucleotides (ISIS-17709) has ten 2'-deoxy nucleosides flanked by two wing segments, each having five 2'-O-methoxyethyl modifications. ISIS-17709 has two 5-methyl cytosines and has natural phosphodiester bonds at the first four and last four linkages with the remainder being phosphorothioate linkages.

ISIS-104838 has ten 2'-deoxy nucleosides flanked by two wing segments, each having five 2'-O-methoxyethyl modifications. ISIS-104838 has phosphorothioate linkages and four 5-methyl cytosines.

ISIS-28089 has twelve 2'-deoxy nucleosides flanked by two wing segments, each having four 2'-O-methoxyethyl modifications. ISIS-28089 has phosphorothioate linkages and six 5-methyl cytosines.

ISIS-17709 and ISIS-104838 are the only two examples of specific oligonucleotides that have ten 2'-deoxy nucleosides flanked by two wing segments, each having five 2'-O-methoxyethyl modifications. ISIS-28089 is the only example of a specific oligonucleotide that has twelve 2'-deoxy nucleosides flanked by two wing segments, each having four 2'-O-methoxyethyl modifications. These specific oligonucleotides are not sufficient to demonstrate support for the entire genus of molecules recited in the claims. The instant specification offers support for these three specific oligonucleotides, but does not offer support for broad recitation of these specific sizes for the gap and wing segments of the oligonucleotide. From the disclosure of the

instant specification, it is not clear that applicant contemplated all gapmers of this size and configuration of modifications.

Furthermore, the instant claims recite that the oligonucleotide "comprises" a 20-nucleobase portion with either the 5-10-5 or 4-12-4 configuration discussed above. However, the three specific oligonucleotides that fall within these size ranges discussed above certainly do not offer support for oligonucleotides with these size restrictions that comprise further elements.

Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation discussed above.

Response to Claim Rejections - 35 USC § 103

Claims 66, 70-75 and 78-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. (WO 96/40266), in view of Nicklin et al. (WO 98/09633) and Yu et al. (Bioorganic & Medicinal Chemistry, Vol. 4, No. 10, pages 1685-1692, 1996), for the reasons of record as set forth in the office action mailed on 5/2/07.

It is noted that newly added claims 83-98 are rejected because these claims recite the same types of modifications that are taught by the prior art and the specific configuration of the modifications is considered within the realm of routine optimization, as explained further below.

Applicant asserts that the amended claims recite that the gap segment consists of ten or twelve contiguous 2'-deoxy nucleosides flanked by 5' and 3' wing segments,

wherein each of the wing segments consists of five or four 2'-methoxyethyl nucleosides, respectively and that these limitations are not taught by any of the cited references.

Although applicant argues the specific number of nucleotides present in the oligonucleotide, gap segment, and wing segments, it was known in the art at the time the invention was made to modify oligonucleotides with gapmer configurations consisting of 2'-deoxy gap segments flanked by 2'-methoxyethyl nucleosides and it was known that hybrid oligonucleotides comprising phosphorothioates and 2'-O-methyl nucleosides have greater activity and are more resistant to nuclease-mediated degradation than oligonucleotides with phosphorothioates only, as evidenced by Yu et al. Certainly one of skill in the art would have been motivated to routinely optimize antisense oligonucleotides other then the 25-mer oligonucleotides of Yu et al. by incorporating the same gapmer concept, 2'-deoxy gap segments flanked by 2'-methyoxyethyl nucleosides, to enhance the activity of these antisense oligonucleotides as well.

The specific number of nucleotides present in the antisense oligonucleotide, as instantly recited, is within the range known to be routine for antisense oligonucleotides. With regards to the specific size of the oligonucleotide, gap segment, and wing segments, it would have been prima facie obvious to perform routine optimization to determine workable sizes, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular sizes used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Applicant argues that Yu et al. teaches away from the instant invention because Yu et al. tested the anti-HIV activity of 8 different 25 base oligonucleotides and reported that the oligonucleotides with the longer central deoxy gap were better than those with the shorter gap or that did not have a central gap. Applicant's interpretation of the teachings of Yu et al. are considered erroneous because the comparison being made by Yu et al. is not a straight comparison of gap size, but is rather a comparison of the activity of gapmers with deoxyribonucleoside phosphorothioates flanked by stretches of 2'-O-methyl ribonucleoside phosphoric diester linkages (oligos 2-4) to hybrid oligonucleotides with deoxyribonucleoside phosphorothioates flanked by segments of contiguous 2'-O-methyl ribonucleoside phosphorothioate linkages (oligo 6). Furthermore, Yu et al. teaches that different configurations have shown preferential results, included inverted hybrids and conclude that the studies demonstrate that it is possible to perform therapeutic optimizations of the antisense oligonucleotides by subtle structural changes in the nucleoside sugar residue and internucleotidic phosphate linkages of the active molecule. Yu et al. further concludes that knowledge gained from these studies should help guide the development of future generation of antisense oligonucleotides as therapeutic agents (see page 1691, column 1). Therefore, the teachings of Yu et al. support that the number of nucleotides of the wings and gaps, as

well as configurations of known modifications in general, are considered to be routine optimizations.

Applicant asserts that in addition, one must modify Yu to replace the 2'-O-methyl wings with 2'-O-methoxyethyl wings as claimed. Applicant asserts that Nicklin discloses more than 90 different 2'-modifications on page 4 and that the examiner has not given a reason why one would choose the recited 2'-O-methoxyethyl modifications. Nicklin et al. specifically teaches an "especially preferred embodiment" wherein the oligonucleotide is a chimeric oligonucleotide having one or more regions with 2'-deoxynucleotides and one or more regions with 2'-modified nucleotides, preferably 2'-alkoxynucleotides, wherein the one or more deoxynucleotide regions preferably have phosphorothioate backbone linkages. Nicklin teaches that these chimeric oligonucleotides preferably comprise a region of 2'-deoxynucleotides flanked by two regions of 2'-modified nucleotides (see pages 4 and 5).

Nicklin et al. teach antisense oligonucleotides and teach that modification of antisense oligonucleotides confers increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target (see page 2). Nicklin et al. teach 2' modifications including 2'-alkoxyalkoxy, 2'-O-methoxyethyl, and 2'-O-dialkylaminooxyalkyl modifications. Nicklin et al. teach phosphorothioate, methylphosphonate, and non-phosphorous containing linkage modifications (see pages 4 and 5). Nicklin et al. teach that preferred bases include 5-methylcytosines (see page 4).

Applicant points to the examiner's statement in the office action mailed on 5/2/07 that "Applicant's arguments and/or amendments filed on 3/26/07, with respect to the rejections under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, these rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the instant amendments." Applicant concludes that therefore the examiner found applicant's arguments to be persuasive. Applicant's interpretation of the examiner's statement is erroneous. As stated in the passage, applicant's "arguments and/or amendments" had been considered and were found persuasive with regards to the rejections under 35 U.S.C. 103(a). The amendment to the claims made by applicant was considered to overcome the rejections of record. As also stated in the above passage, a new ground of rejection was made in view of the amendments. Applicant had amended the claims to recite gapmer configurations and therefore necessitated an additional piece of art, the Yu et al. reference. Therefore, applicant's assertions regarding the basis of the withdrawal of the earlier pending rejections is in error and is completely inapplicable to the instant rejection.

In conclusion, it is maintained that it was known in the art at the time the invention was made to formulate respirable antisense oligonucleotides for administering the oligonucleotide to the lung, as evidenced by Nyce et al.; it was known that it is preferred to chemically modify antisense oligonucleotides for enhanced delivery with the instantly recited modifications, as evidenced by Nyce et al., Nicklin et al., and Yu et al.; and it was known that gapmer configurations are preferential for enhanced activity

antisense oligonucleotides, as evidenced by Nicklin et al. and Yu et al. Since the delivery method of aerosolizing the oligonucleotide was known, each of the chemical modifications were known, and it was known to incorporate known modifications into gapmer configurations, simply determining a specific number of nucleotides for the oligonucleotide, gap segment, and wing segments is considered within the realm of routine optimization.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

New Objections/Rejections

Claim Objections

Claim 92 is objected to because of the following informalities: Claim 92 does not end with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 66, 70-75, and 78-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 66, 78 and 89 recites the limitation "said first and second wing segments". There is insufficient antecedent basis for this limitation in the claim. Recitation of "said first wing segment and said second wing segment", for example, would obviate this rejection.

Claims 70-75, 79-88 and 90-98 are rejected because they depend from claims 66, 78 or 89.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H. Bowman
Examiner
Art Unit 1635

AHB

/J. E. Angell/
Primary Examiner
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